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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/845,623	04/30/2001	Sudhir Agrawal	47508.528	2601

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KEOWN & ASSOCIATES
500 WEST CUMMINGS PARK
SUITE 1200
WOBURN, MA 01801

EXAMINER	
MCINTOSH III, TRAVISS C	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 02/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/845,623	AGRAWAL ET AL.	
	Examiner	Art Unit	
	Traviss C McIntosh	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-24 and 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-24 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Amendment filed November 24, 2004 has been received, entered into the record, and carefully considered. The following information provided in the amendment affects the instant application by:

Claims 18-24 and 27 are pending.

Remarks drawn to rejections of Office Action mailed July 28, 2004 include:

112 2nd paragraph rejections: which have been maintained for reasons of record.

112 1st paragraph rejections: which have been maintained for reasons of record.

An action on the merits of claims 18-24 and 27 is contained herein below. The text of those sections of Title 35, US Code which are not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

The rejection of claims 18-24 and 27 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing an immune response comprising administering a compound comprising a CpG dinucleotide and an immunomodulatory moiety wherein the immunomodulatory moiety is: 2'-deoxyuridine which is 2 nucleosides in either the 3' or 5' direction of the CpG dinucleotide, or an abasic nucleoside which is 4 or 5 nucleosides in the 5' position of the CpG dinucleotide, does not reasonably provide enablement for a method of inducing an immune response comprising administering a compound comprising a CpG

dinucleotide and an immunomodulatory selected from the group consisting of one or more abasic nucleoside, l,3-propanediol linker which may be substituted or unsubstituted, 3'-3' linkage and a modified base-containing nucleoside, wherein the modified base-containing nucleoside is selected from the group consisting of inosine, 2-amino-purine, nebularine, 7-deaza-guanosine, nitropyrrole, nitroindole, deoxyuridine, 4-thio-deoxyuridine, d-isoguanosine, d-iso-5-methylcytosine and P-base is maintained for reasons of record. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in ***In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)***. A conclusion of lack of enablement means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

These factors include:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims - The nature of the invention

Claim 18 is drawn to a method for inducing an immune response in a mammal comprising: administering to the mammal a compound comprising a CpG dinucleotide and an immunomodulatory moiety wherein the immunomodulatory moiety is selected from the group consisting of: one or more abasic nucleosides, a 1,3-propanediol linker which may be substituted or unsubstituted, a 3'-3' linkage, and a modified base containing nucleoside, wherein the modified base containing nucleoside is selected from the group consisting of: inosine, 2-amino-purine, nebularine, 7-deaza-guanosine, nitropyrrole, nitroindole, deoxyuridine, 4-thio-deoxyuridine, d-isoguanosine, d-iso-5-methylcytosine, and P-base; and wherein the compound has a greater immunostimulatory effect than it would if it lacked the immunomodulatory moiety. Claim 19 limits the animal to a human, claim 20 limits the route of administration. Claims 21 and 22 provide an amount of active agent to be taken. Claim 23 provides that the compound is taken in combination with a vaccine, and claim 24 additionally adds an adjuvant. Claim 27 limits G of the CpG dinucleotides to guanosine, 7-deazaguanosine, or inosine.

The state of the prior art

CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) are known to induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555, WO 99/33488 and U.S. Pat. Nos. 6,008,200 and 5,856,462. Phosphorothioate CpG containing oligonucleotides are known to be immunostimulatory (Hutcherson et al. US Patent 5,663,153). Liang et al. teach that phosphorothioate CpG containing oligonucleotides are known to activate human B cells (J. Clin. Invest. 98:1119-1129, 1996). Moldoveanu et al. teach phosphorothioate CpG containing

oligonucleotides enhance immune response against influenza virus (Vaccine, 16:1216-124, 1998). Moreover, the various modified nucleosides and linkages are known in the art. Yu et al. (Exhibit 3 of declaration filed April 19, 2004) shows that the position of immunomodulatory moieties in relation to the CpG dinucleotide are critical to immunostimulatory function (see abstract). Additionally, Agrawal et al. (US Patent 5,968,909) shows that modification of C or G in the CpG dinucleotide suppresses the immunostimulatory effects of the CpG dinucleotide.

The level of predictability in the art

The examiner acknowledges the probability and predictability that CpG containing oligonucleotides have immunomodulatory activity. The examiner also acknowledges that phosphorothioate oligonucleotides provide immune stimulation. The art teaches that the location of the immunomodulatory agent is critical for immunostimulatory activity (see Yu et al.). The art is silent with regard to the predictability that any of the cited immunomodulatory moieties are effective in combination with a CpG dinucleotide at inducing an immune response when they are in any location. Moreover, physiological activity of compounds *in vitro* is not indicative of the same activity *in vivo*.

The amount of direction provided by the inventor

The instant specification is not seen to provide adequate guidance which would allow the skilled artisan to extrapolate from the disclosure and examples provided to use the claimed method commensurate in the scope with the instant claims. There is a lack of data and examples which adequately represent the scope of claim as written. The examiner notes, there has not been provided sufficient instruction or sufficient methodological procedures to support the alleged efficacy of prevention instantly asserted.

The existence of working examples

The working examples set forth in the instant specification are drawn to the following examples:

Example 1: an in vitro test using mouse spleen lymphocytes cultured with oligonucleotides to determine cell proliferation levels.

Example 2: an in vivo test comprising intraperitonealy administering oligonucleotides to mice and determining spleen weights.

The results shown in figure 2 show that oligonucleotide 131-12 was the only oligonucleotide which is seen to have an increased immunostimulatory effect as compared to the control and oligonucleotide 131-1. Sample 131-1, which comprised a CpG dinucleotide sequence and no immunomodulatory moiety, and 131-13 which comprised a modified C of the CpG dinucleotide sequence showed results similar to that of the control, PBS. The results shown in figure 3 are correlative to those for figure 2, and the only oligonucleotide with increased immunostimulatory effect when compared to the control is sample 133-12, which comprises abasic nucleosides 3 and 4 nucleosides on the 5' side of the CpG dinucleotide.

Moreover, in applicants declaration filed 4/19/2004, they attempted to present evidence showing that additional immunomodulatory moieties have immunostimulatory effects when coupled with a CpG dinucleotide. However, in review of the evidence provided, the examiner has concluded that applicants have failed to show enablement for the broad genus as claimed. For example, applicants showed in figure 1 of exhibit 2 that all three oligonucleotides (105-5, 113-1, and 105-8) showed correlative immunostimulatory effects when compared each other. Thus, the 2'-deoxynitropyrrole moieties (in 105-5 and 105-8) did not add anything to the

immunostimulatory effects of the CpG containing sample of 113-1. All three oligonucleotides exhibited correlative results, and yet, only two of the oligonucleotides had the 2'-deoxynitropyrrole moiety included therein. Additionally, Figure 2B shows that three phosphorothioate oligonucleotides (113-1, 121-2, and 121-4) have correlative immunostimulatory effects *in vivo*, while figure 2A shows that both 121-2 and 121-4 (phosphorothioate oligonucleotides with 2'-deoxyuridine moieties 2 positions down from the CpG function in either the 3' or 5' direction) have an increased immunostimulatory effect *in vitro* when compared to 113-1 (phosphorothioate oligonucleotide without the 2'-deoxyuridine moiety).

There has not been provided sufficient evidence which would warrant the skilled artisan to accept the data and information provided in the working examples as correlative proof that a compound comprising a CpG dinucleotide and any of the claimed immunomodulatory moieties indeed has efficacy as instantly asserted.

The quantity of experimentation needed to make and use the invention based on the content of the disclosure

Indeed, in view of the information set forth supra, the instant disclosure is not seen to be sufficient to enable a method of inducing an immune response in a mammal comprising administering a compound comprising a CpG dinucleotide and any of the claimed immunomodulatory moieties as instantly asserted. One skilled in the art could not use the entire scope of the claimed invention without undue experimentation.

Enablement for a single compound cannot provide enablement for the breadth of claims sought in arts which are unpredictable. That is, a single embodiment may provide broad

enablement in cases involving predictable factors, but more is required in cases involving unpredictable factors, such as chemical or physiological activity. See ***Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987)*** and ***In re Shokal, 242 F.2d 771, 113 USPQ 283, 285 (CCPA 1957).***

Applicant's arguments filed November 24, 2004 have been fully considered but they are not persuasive. Applicants argue that all of the oligonucleotides used were PS-oligonucleotides, which is seen to be convincing in that it is not the PS moiety which is adding the immunostimulatory effect. Moreover, applicants state that while the Yu et al. reference states the location of the immunostimulatory moiety in respect to the CpG dinucleotide is critical, applicants believe that the Yu et al. reference is not the state of the art at the time of the invention, as the Yu et al. reference published after the filing date of the instant application. However, the examiner believes that the Yu et al. reference is indeed the state of the art at the time of the invention. Yu et al. states that "the presence of a CpG dinucleotide sequence with specific nucleotides in the flanking sequences is critical for the immunostimulatory activity of the CpG-DNAs" and cites references dated from 1995, 1992, and 1994. Yu et al. additionally state that "our earlier studies have shown that sugar or backbone modifications within a CpG dinucleotide neutralized the immunostimulatory activity and the same modifications distal to the CpG dinucleotide did not neutralize the immunostimulatory activity of the CpG DNA", wherein Yu et al. cited references from 1996, 1999, 2000, and 2001. Thus, the state of the art from 1992 until the publication of the Yu et al. reference show that the location of the immunomodulatory moiety in the CpG DNA indeed is critical to the activity of the same.

Claims 18-24 and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection of claim 18 for being indefinite as being drawn to a 1,3-propanediol linker which may be "substituted", wherein there is no identification on how applicant intends to "substitute" the linker in the claims, is maintained for reasons of record. In the absence of the identity of moieties which are intended to be substituted, thus altering an art recognized chemical core, described structurally or by chemical name, the identity of "substituted" would be difficult to ascertain. In the absence of said moieties, the claims containing the term "substituted" without defining what is to be "substituted" are not described sufficiently to distinctly point out that which applicant intends as their invention. Applicants argue that the specification defines "substituted" at page 13, lines 1-31. However, it is noted that page 13, lines 1-31 of the specification are drawn to various substitutions which are contemplated for the base, and not the linker (i.e., 2'-O-substituted, and 3'-O-substituted moieties). Nowhere in the specification is there seen to be adequate guidance as to what is intended to be substituted on the 1,3-propanediol linker, nor where on the linker the substitutions are to occur. One of skill in the art would not be appraised to the metes and bounds of the claim drawn to "substituted linkers" when read in light of the specification.

All claims which depend from an indefinite claim are also indefinite. ***Ex parte Cordova, 10 U.S.P.Q. 2d 1949, 1952 (P.T.O. Bd. App. 1989).***

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Traviss C McIntosh whose telephone number is 571-272-0657. The examiner can normally be reached on M-F 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Traviss C. McIntosh III
February 22, 2005

James O. Wilson
Supervisory Patent Examiner
Art Unit 1623